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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/937,837	Applicant(s) DALBY ET AL.	
	Examiner Daniel M Sullivan	Art Unit 1636	

-- Th MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *2-11,18,29,30,37,42-45 and 47-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-11,18,29,30,37,42-45 and 47-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7 and 8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This is a First Office Action on the Merits of the Application filed January 7, 2002, which is a U.S. National Stage Application of PCT/US00/08571, filed March 31, 2000, and claims benefit of U.S. Provisional Application 60/127,467, filed March 31, 1999. This Action is a response to the Response to Restriction Requirement filed August 19, 2002 (Paper No. 11) and Information Disclosure Statements filed September 28, 2001 (Paper No. 7) and January 8, 2002 (Paper No. 8). Claims 1-50, as originally filed, are pending in the application.

Election/Restrictions

Applicant's election of Group III, claims 1, 12-17, 19-28, 31-36, 38-41 and 46 in Paper No. 11 is acknowledged. Because applicant did not distinctly and specifically point out errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 2-11, 18, 29, 30, 37, 42-45 and 47-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 11.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Drawings

The drawings are objected to for the reasons provided on the attached PTO-948. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 12-14, 17, 19-28, 31-36, 38-41 and 46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The claims of the instant Application are drawn to a method for modulating a cellular process or expression of a target gene in cell culture comprising contacting a cell in culture with a cell process-modifying molecule or regulatory agent attached to a translocating polypeptide. Given their broadest reasonable interpretation the claims encompass methods of using any and

all translocating polypeptides. The Revised Interim Guidelines state "The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (Column 3, page 71434). In the instant case, the translocating polypeptide is a critical element in the claimed method; therefore it is incumbent upon Applicant, under 35 USC 112, first paragraph, to provide an adequate description of the translocating polypeptide. According to the definition provided on page 6 of the specification, "the term 'translocating protein' means a protein, polypeptide or functional fragment thereof, that crosses biological membranes...[possessing] the following properties: resistance to proteolysis, receptor-independent penetration of cell membranes, and substantially energy-free penetration of cell membranes". Therefore the genus encompassed by the translocating polypeptide of the claims includes any and all polypeptides having the aforementioned properties.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics (see MPEP 2163 (ii)). In the instant case, the disclosure provides three species of translocating polypeptides (i.e. Herpes Simplex Virus VP22, a fragment of the Drosophila Antennapedia protein, and the Streptococcus pyogenes Protein H) and reduction to practice of the claimed method wherein the translocating polypeptide is VP22. The teachings of the specification are not, however, sufficient to provide the common attribution of the genus of any and all translocating polypeptides. Teachings in the prior art published subsequent to the filing date of the instant Application indicate that the structural characteristics that confer upon a peptide or protein the properties of

the instant translocating polypeptide were not known at the time the instant application was filed. For example, in 2001 Falnes *et al.* (*Biochemistry* 40:4349-4358) teach that, "virtually nothing is known regarding the mechanism of cellular targeting or membrane penetration by [proteins such as TAT or Antennapedia]" (page 4350, first full paragraph). In 2000, Schwarze and Dowdy (*Trends Pharmacol* 21:45-48) teach that, "structural comparisons between known [protein transduction domains] provide little insight into the mechanism of transduction" (second full paragraph of column 3 on page 45) and Schwarze *et al.* (*Trends. Cell Biol.* 10:290-295) teach that, "the mechanism whereby these [protein transduction domains] are able to target and to traverse lipid membranes currently remains unknown. In fact, more is known about how protein transduction does not work than how it does work" (second full paragraph of column 2 on page 290). These teachings demonstrate that, at the time of filling, one of ordinary skill in the art would not be able to correlate the functional properties of a translocating polypeptide, as the term is defined in the instant Application, with structural characteristics and thus would not be able to recognize a translocating polypeptide based on the structure of said translocating polypeptide. The specification is mostly silent with regard to the structural properties of a translocating polypeptide and therefore does not remedy the deficiencies taught by the prior art.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of *any* and *all* translocating polypeptides. Therefore, only the described VP22, Antennapedia and Protein H polypeptides meet the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1, 12-17, 19-28, 31-36, 38-41 and 46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for modulating a cellular process or expression of a target gene in a cell comprising contacting a cell in culture with a cell process-modifying molecule or regulatory agent attached to a translocating polypeptide, wherein: the plasma membrane of said cell is not enclosed within a cell wall; the translocating polypeptide is VP22 polypeptide, Antp or Protein H; and the regulatory agent is T7 RNA polymerase, HIV Rev protein, rhoA, or Flp, does not reasonably provide enablement for methods of modulating a cellular process in any and all cells or with any and all translocating polypeptides attached to any and all cell-process modifying molecules or regulatory agents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or

use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention: The instant invention is drawn to methods of modulating a cellular process or expression of a target gene wherein a modulatory molecule is linked with a peptide or protein that facilitates the movement of said regulatory molecule across the plasma membrane of cell.

Breadth of the claims: Given their broadest reasonable interpretation, the claims encompass a method of modulating a cellular process wherein any molecule capable of modulating a process within a cell, and particularly the process of gene expression, is fused with any molecule capable of facilitating transport of another molecule across a cell plasma membrane and introduced into any cell, including plant and other cells comprising a cell wall, such that a cellular process or expression of a target gene is modulated.

State and Level of predictability in the art: The teachings of the prior art cited herein above with regard to the written description of translocating polypeptides demonstrate, in part, the unpredictability that remained in the relevant art even after the effective filing date of the instant Application. To summarize, those teachings point out that it was not possible, at the time the instant invention was made, to possess or make a translocating polypeptide without empirical experimentation. One of ordinary skill could not predict, based on the teachings of the specification or prior art, the structure that would provide the desired function. Furthermore, the same art teaches that even if the skilled artisan could provide any and all translocating polypeptides without undue experimentation, a high degree of unpredictability remains in practicing the claimed method commensurate with the scope of the claims. This is because

empirical evidence suggests that many proteins are denatured in the process of translocation by a translocating polypeptide. For example, Schwarze *et al.* (*supra*) teaches that, "transduction of full-length TAT-PTD fusion proteins across the cell membrane results in an inactivation or denaturation of the protein...These observations suggest that transduction across the cellular membrane is a stringent process that partially or completely unfolds a protein and this then needs refolding *in vivo*" (page 290, column 2, first full paragraph) and "[f]rom the limited data currently available, transduction across the cellular membrane is thought to result in a partial or complete unfolding of the protein that will probably differ from one protein to another. Therefore, once inside the cell, the transduced protein requires refolding to obtain biologically active protein" (page 294, column 2, second full paragraph). Further, Schwarze and Dowdy (*supra*) teach, "[i]t is important to note that not all proteins are the same and, therefore, one protocol will not work for all proteins" (page 46, column 3, second full paragraph). These teachings demonstrate that the successful application of the claimed method with any given modulatory molecule is dependent upon the ability of said modulatory molecule to renature inside of the cell once it has been translocated across the plasma membrane. Predicting whether or not a given molecule will be capable of renaturing once denatured in the process of translocation and thus of modifying a cellular process or modulating expression of a target gene is beyond the capabilities of the ordinary skilled artisan.

Additionally, there are clearly limits on the molecules that can be transported across the plasma membrane by known translocating polypeptides. For example, Kueltzo and Middaugh (2000) *Exp. Opin. Invest. Drugs* 9:2039-2050 teach that, for Antennapedia, "[t]he cargo is primarily size limited" (page 2042, third full paragraph).

Finally, although the teachings of the relevant art do not yet provide a mechanism for entry of translocating polypeptides into the cell, the skilled artisan would not predict, based on what is known to date, that the method as claimed would work in cells wherein the plasma membrane is encased within a cell wall (i.e. plant cells and prokaryotic cells). First, the prior art does not provide an example of a translocating polypeptide capable of crossing a cell wall. Next, the theories put forward based on the available data obtained thus far (such as the "Molten globule states" or "Inverted micelle formation" taught by Kueltzo and Middaugh beginning on page 2044 and continued through the first full paragraph on page 2045) do not suggest that a translocating polypeptide would be capable of crossing a cell wall.

Therefore, based on the teachings of the prior art, the skilled artisan would not predict success in practicing the invention commensurate with the full scope of the claims.

Amount of direction provided by the inventor and existence of working examples: The teachings of the specification provide a detailed description of three translocating polypetides, and provide working examples of the claimed invention wherein the VP22 protein is fused to the site-specific recombinase Flp, HIV Rev protein, rhoA and T7 RNA polymerase wherein the requisite modulation of a cellular process or expression of a target gene product is observed (see especially Examples 5-8).

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: The relative level of skill in the art is very high; however, given that the teachings of the prior art and specification do not provide a means to overcome the potential barriers to practicing the claimed invention with any and all translocating polypetides (i.e. the lack of understanding regarding the structural features that provide the desired properties), or any and all

cell process-modifying molecules or regulatory agents (i.e. the potential for inactivation of proteins in the process of translocation), or any and all cells (i.e. the need to cross the cell wall of plants and prokaryotes), the skilled artisan would have to engage in empirical experimentation to address each of these problems as they arise in the method practiced with any given combination of translocating polypeptide, process-modifying molecule or regulatory agent, and cell. Practicing the invention commensurate with the full scope of the claims would therefore require that the skilled artisan engage in undue experimentation.

Claims 32-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed to a method which comprises a cell line that contains a single genomic recombination site. Lewin (*in* Genes III (1987) Wiley & Sons, Inc., New York) teaches that the enzymes responsible for generalized recombination "can use *any* pair of homologous sequences as substrates" (page 563, paragraph 3). Therefore any structure made up of DNA comprises multiple recombination sites, the identity of which is dictated by the presence or absence of a homologous sequence. In other words, any cellular genome comprises an almost infinite number of potential recombination sites. Even when the recombinase used is limited to the site-specific recombinases Cre or Flp, Silver *et al.* (Pub. No.: US 2002/0062489 A1) teach that it is likely that mammalian genomes contain a number of endogenous sequences that can function as targets for cre (see especially paragraphs [0030] and [0031] and citations therein). Based on these teachings, and the absence of guidance in the specification as to how to obtain a

cell containing a single genomic recombination site the skilled artisan would not predict that it would be possible to obtain such a cell without undue experimentation to identify a cell line with a single recombination site or to eliminate all but one recombination site from the genome of a cell line.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 46 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim is indefinite in that it limits the claimed method to a method wherein the cell is "refractory" to other transfection techniques without defining the metes and bounds of the term refractory. According to the Merriam-Webster definition, the limitation would simply mean that the cell is resistant to another transfection technique. It would seem logical that all cells are resistant to transfection techniques such as contacting cells with naked DNA to some extent. It is unclear from the disclosure, however, at what point the resistance meets the claim limitation. If given its broadest reasonable interpretation, the limitation would encompass all cells and therefore fails to further limit the base claim. For the purpose of determining patentability of the claim over the prior art, the limitation will be given its broadest reasonable interpretation.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 12-15, 17, 25-27 and 46 rejected under 35 U.S.C.§102(a) as being anticipated by Pooga *et al.* (September 1998) *Nat. Biotechnol.* 16:857-861.

Claim 1 is directed to a method for modulating a cellular process, said method comprising contacting a cell in culture under suitable conditions with a cell process-modifying molecule attached to a translocating polypeptide, whereby the cell process-modifying molecule is translocated into the cell in culture and interacts specifically therein with a target site responsive to the cell process-modifying molecule, thereby modulating a cellular process in the cell in culture.

Pooga *et al.* teach a method for modulating expression of a human galanin receptor comprising, contacting a cell in culture under suitable conditions with a cell process-modifying peptide nucleic acid molecule attached to a translocating polypeptide, whereby the cell process-modifying molecule is translocated into the cell in culture and interacts specifically therein with a target site responsive to the cell process-modifying molecule (i.e. the endogenous RNA encoding the galanin receptor), thereby modulating expression of the galanin receptor in the cell in culture (see especially Figure 2 and the caption thereto, and Table 1).

Claim 12, and claims 13-15, 17, 25-27 and 46 as they depend from claim 12, are directed to a method for modulating expression of a target gene product in a cell in culture that contains a target gene under control of one or more regulatory elements, said method comprising contacting the cell in culture under suitable conditions with one or more regulatory agents attached to a translocating polypeptide, whereby the one or more regulatory agents are translocated into the

cell in culture and interact therein with the one or more regulatory elements, thereby modulating expression of the target gene product by the cell.

For the purpose of determining patentability of the claims over the prior art, the limitation "regulatory element" has been interpreted to broadly encompass any element capable of regulating expression of a gene. In the case of Pooga *et al.*, the suppression of galanin receptor expression upon translocation of the PNA complex indicates interaction with a regulatory element, likely at the level of protein translation.

Claim 13 is directed to the method according to claim 12 wherein the cell in culture is a mammalian, yeast, insect or plant cell.

Pooga *et al.* teach the method in human Bowes melanoma cells (see especially the second paragraph on page 858).

Claim 14 is directed to the method according to claim 12 wherein the translocating polypeptide has the properties of resistance to proteolysis, receptor-independent penetration of cell membranes, and energy-independent penetration of cell membranes; claim 15. limits method according to claim 12 to a method wherein the translocating polypeptide is a VP22 polypeptide, Antp, or Protein H.

Pooga *et al.* teach a method wherein the translocating polypeptide is Antp (see especially the second paragraph on page 858).

Claim 17 is directed to the method according to claim 12 wherein the regulatory agent is a polynucleotide, a protein or polypeptide, or a small molecule; claim 25 is directed to the method according to claim 12 wherein the regulatory agent and the translocating polypeptide are covalently attached; claim 26 is directed to the method according to claim 12 wherein the

regulatory agent and the translocating polypeptide are attached by a linker and claim 27 is directed to the method according to claim 26 wherein the linker comprises one or more disulfide bonds, salicylhydroxamic acid (SHA), phenylboronic acid (PBA), a SHA-NHS ester, or a combination thereof.

Pooga *et al* teach a method wherein the regulatory agent is a polynucleotide that is covalently attached by a linker which comprises a disulfide bond (see especially the third paragraph on page 860).

Claim 46 is drawn to the method according to claim 12 wherein the cell is refractory to other transfection techniques. As indicated herein above, this limitation has been interpreted to encompass all cells, and therefore the cells of Pooga *et al.* read on the claim.

The method for modulating a cellular process or expression of a target gene product in a cell in culture, cell, translocating polypeptide, regulatory agent and linker taught by Pooga *et al.* are the same as those taught in the instant application; therefore the limitations of the claims are met by Pooga *et al.*

Claims 1, 12-17, 19, 20, 24, 25, 28. 40 and 46 are rejected under 35 U.S.C.§102(a) as being anticipated by Phelan *et al.* (May 1998) *Nat. Biotechnol.* 16:440-443.

The limitations of claims 1, 12-15, 17, 25 and 46 are recited above.

Phelan *et al.* teach a method for modulating apoptosis comprising, contacting a cell in culture under suitable conditions with a cell process-modifying p53 molecule attached to a translocating polypeptide, whereby the cell process-modifying molecule is translocated into the cell in culture and interacts specifically therein with a target site responsive to the cell process-

modifying molecule (i.e. p53 regulatory elements), thereby modulating expression of p53 responsive genes in the cell in culture (see especially page 442 and Figures 3 and 5 and the captions thereto). Therefore, the method of Phelan *et al.* anticipates claim 1.

The method of Phelan *et al.* provides a means to regulate expression of a target gene product in a cell in culture that contains a target gene under control of a p53 regulatory element according to the method of claim 12, wherein: said cells are human SAOS-2 osteosarcoma cells according to the method of claim 13 and 46 (see especially the third full paragraph on page 441); said regulatory agent is a protein according to claim 17; said regulatory agent and said translocating polypeptide are covalently attached according to the method of claim 25; and said translocating polypeptide is VP22 according to the methods of claims 14, 15 and 16 (throughout).

Claim 19 is directed to he method according to claim 14 wherein the regulatory element is a promoter and translocation of the regulatory agent transactivates expression of the target gene product by the promoter; claim 20 is directed to the method according to claim 19 wherein the regulatory agent is specific for the promoter; and claim 24 is directed to the method according to claim 12 wherein the regulatory agent is a transcription factor specific for the regulatory element and translocation of the regulatory agent transactivates expression of the target gene product.

Phelan *et al.* teaches a method wherein the regulatory element is a p53 responsive promoter, specific for regulatory agent p53, and translocation of the regulatory agent transactivates expression of the target gene product as evidenced by the apoptotic response in SAOS-2 cells (see especially figures 3 and 5 and the captions thereto).

Claim 28 is directed to the method according to claim 12 wherein the translocating polypeptide and the regulatory agent are units of a fusion protein.

The regulatory agent of Phelan *et al.* is produced as a fusion protein with the translocating polypeptide (see especially Figure 1 and the caption thereto).

The method for modulating a cellular process or expression of a target gene product in a cell in culture, cell, translocating polypeptide, regulatory agent, and regulatory agent-translocating polypetide fusion protein taught by Phelan *et al.* are the same as those taught in the instant application; therefore the limitations of the claims are met by Phelan *et al.*

Claims 12 and 40 are rejected under 35 U.S.C.§102(a) as being anticipated by Phelan *et al.*(*supra*) as evidenced by Schuler and Green *Biochem. Soc. Transact.* (2001) 29:684-688.

The limitations of claim 12 are recited herein above as are relevant teachings of Phelan *et al.*

Claim 40 is directed to the method according to claim 12 wherein the target gene encodes a toxic protein. Schuler and Green teach that the p53 responsive genes that p53 responsive genes, the expression of which would be induced in the method of Phelan *et al.*, include such toxic proteins as Bax, Noxa or PUMA (see especially the first column on page 684, approximately three-quarters down). Therefore, the method taught by Phelan *et al.* is the same as the method of claim 40, wherein the target gene encodes a toxic protein.

Claims 1, 12-15, 17, 25-27 and 46 rejected under 35 U.S.C.§102(b) as being anticipated by Allinquant *et al.* (1995) *J. Cell Biol.*. 128:919-927.

The limitations of the claims are recited above.

Allinquant *et al.* teach a method for modulating expression of amyloid precursor protein comprising, contacting a cell in culture under suitable conditions with a cell process-modifying peptide nucleic acid molecule attached to a translocating polypeptide, whereby the cell process-modifying molecule is translocated into the cell in culture and interacts specifically therein with a target site responsive to the cell process-modifying molecule (i.e. the endogenous RNA encoding the amyloid precursor protein), thereby modulating expression of the amyloid precursor protein in the cell in culture (see especially Figure 3 and the caption thereto, and the paragraph bridging columns 1 and 2 on page 922). The method of Allinquant *et al.* anticipates the method of claim 1.

Claim 12, and claims 13-15, 17, 25-27 and 46 as they depend from claim 12, are directed to a method for modulating expression of a target gene product in a cell in culture that contains a target gene under control of one or more regulatory elements, said method comprising contacting the cell in culture under suitable conditions with one or more regulatory agents attached to a translocating polypeptide, whereby the one or more regulatory agents are translocated into the cell in culture and interact therein with the one or more regulatory elements, thereby modulating expression of the target gene product by the cell.

Allinquant *et al.*, teach the above method wherein the suppression of amyloid precursor protein expression upon translocation of the PNA complex indicates interaction with a regulatory element, likely at the level of protein translation. The method of Allinquant *et al.* therefore anticipates claim 12, and claims 13-15, 17, 25-27 and 46 as they depend from claim 12.

Allinquant *et al.* teach the method in rat fetal neurons (see especially the second paragraph on page 920), which anticipates the limitations of claim 13 and 46; the method wherein the translocating polypeptide is Antp (see especially the third paragraph on page 920), which anticipates the limitations of claims 14 and 15; the method wherein the regulatory agent is a polynucleotide that is covalently attached by a linker which comprises a disulfide bond (see especially the third paragraph on page 920), which anticipates the limitations of claims 17, 25 and 26.

The method for modulating a cellular process or expression of a target gene product in a cell in culture, cell, translocating polypeptide, regulatory agent and linker taught by Allinquant *et al.* are the same as those taught in the instant application; therefore the limitations of the claims are met by Allinquant *et al.*

Claim 1 is rejected under 35 U.S.C.§102(b) as being anticipated by Lissy *et al.* (January 1998) *Immunity* 8:57-65.

The limitations of the claim are recited above. Lissy *et al.* teach a method for modulating pRB activity comprising, contacting a cell in culture under suitable conditions with a cell process-modifying human papillomavirus E7 protein attached to a translocating polypeptide, whereby the cell process-modifying molecule is translocated into the cell in culture and interacts specifically therein with a target site responsive to the cell process-modifying molecule (i.e. pRB), thereby modulating pRB activity in the cell in culture (see especially the first full paragraph on page 61 and the third full paragraph in the second column on page 64). The method of Lissy *et al.* therefore anticipates the method of claim 1.

Conclusion

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
October 30, 2002

JAMES KETTER
PRIMARY EXAMINER